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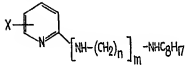
(54) BIOCIDAL PYRIDINE DERIVATIVES

(71) We, TH. GOLDSCHMIDT A.G., a body corporate organised under the Laws of Germany, of 100 Goldschmidtstrasse, 43 Essen, Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement: —

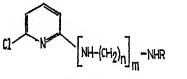
This invention relates to new biocidal pyridine derivatives of the general formula I



I

wherein X is a hydrogen atom or is a bromine atom which may be in the 5 or 6 position of the pyridine ring, n is 2 or 2 and m is 0, 1 or 2.

In the Specification of our Patent No. 1,298,054 compounds with a chemically similar structure of the general formula II have been described

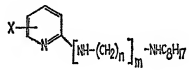


II

wherein R is an alkyl radical containing 8 to 18 carbon atoms, n is 2 or 3 and m is 1 or 2.

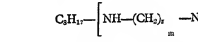
The compounds of formula II are valuable biocides, and it might be assumed that the compounds of formula I would also have some biocidal effects. It was not to be expected however, and was therefore particularly surprising, that the compounds of formula I would exhibit a yet appreciably better bacteriological effectiveness and a yet smaller irritation effect on the skin and the mucous membranes than the compounds of formula II. In view of these advantageous properties, the present compounds of formula I are far superior to commercial biocides, such as phenols or quaternary ammonium compounds.

An aspect of the present invention provides a process for the preparation of a compound of the general formula



where X is a hydrogen atom or a bromine atom which may be in the 5 or 6 position of the pyridine ring, n is 2 or 3 and m is 0, 1 or 2, wherein 1 mol of a compound of the general formula

where Y is a chlorine or bromine atom is reacted with 1 to 4 mols of an amine of the general formula



where X, n and m have the meanings defined above, at a temperature of 100 to 180° C. in the presence of an acid acceptor.

The halogenated pyridine reactant may be, for example, 2-chloropyridine, 2-bromopyridine, 2,6-dibromopyridine or 2,5-dibromopyridine.

The reaction may be carried out in the presence of a solvent, such as ethyl alcohol, dioxane, chlorobenzene or propylene glycol, but the use of such a solvent is not necessary. The amine of formula III may be, e.g. octylamine, N-octylpropylenediamine, N-octyldipropylenetriamine or N-octyldiethylenetriamine. Suitable acid acceptors are, e.g., sodium hydroxide potassium hydroxide, calcium hydroxide, sodium carbonate, potassium carbonate or an excess of the amine of formula III.

The present compounds of formula I are preferably used in form of their salts, e.g. as acetates, lactates, tartrates, gluconates, citrates, hydrochlorides, phosphates and nitrates. These salts are water-soluble or water-dispersable. The compounds may be formulated into a biocidal composition with a solid or liquid diluent or carrier for the compound.

In addition it is possible in the manufacture of compositions containing the present compounds to use a solvent such as methanol, ethanol, methyl glycol, ethyl glycol, ethylene glycol, propylene glycol or glycerol, and to incorporate in the composition a non-ionic surfactant such as an ethoxylation product of lauryl alcohol, isotridecyl alcohol, nonyl phenol, isooctyl phenol or a fatty acid glyceride, as well as a copolymer of ethylene oxide and propylene oxide.

These compositions may be of liquid, solid or pasty consistency and they may contain thickeners such as methyl-, hydroxyethyl- and carboxymethyl-cellulose, polyacrylic acid and its derivatives, polyvinyl alcohol, and polyvinyl pyrrolidone, as well as inert fillers such as highly dispersed silica, aluminium oxide, zinc sulphide, titanium dioxide, as well as urea, cane sugar and cellulose and finally also colorants and odorants.

Due to their excellent properties as described above, the present compounds and compositions containing them are particularly suitable for use as disinfecting and preserving agents for use for example in the beverage industry, in dairies, in fish and meat processing undertakings as well as in human and veterinary medicine.

The invention will now be described by reference to the following illustrative Examples of the manufacture of the compounds in accordance with the invention and compositions containing them: —

Example 1

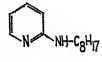
Preparation of

1 mol of 2-chloropyridine, 4 mols of n-octylamine, 1.2 mols of sodium hydroxide and 0.3 mol of water are heated for 15 hours under reflux. The mixture is then cooled and decanted off the inorganic residue while still hot. The organic phase is then subjected to fractionat distillation *in vacuo*. After a first run of n-octylamine, 134 g. of the product in accordance with the invention distil over at 150 to 170°C. and 10^{-1} to 10^{-2} mm.Hg., corresponding to a yield of 65% of the theoretical.

Elemental analysis

Calculated for $C_{12}H_{22}N_2$ (206):	Found
C: 75.7%	C: 75.3%
H: 10.7%	H: 10.9%
N: 13.6%	N: 13.3%

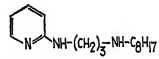
Manufacture of a composition containing



5 parts by weight of the above compound, 10 parts by weight of the addition product of 10 mols of ethylene oxide with 1 mol of lauryl alcohol, 10 parts by weight of acetic acid, 0.5 part by weight of sodium acetate, 20 parts by weight of *n*-propanol and 115 parts by weight of water are homogenized with stirring and slight heating. A clear solution, dilutable with water is obtained.

Example 2

Preparation of

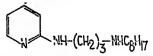


1 mol of 2-chloropyridine, 3 mols of N-n-octylpropylene diamine, 1.5 mols of sodium hydroxide (flakes) and 0.5 mol of water are heated for 20 hours to approximately 160° C.. After analogous treatment to that described in Example 1 and distillation in a molecular distillation apparatus, 155 g. of the pure product of the above constitution distilled at a bath temperature of 100 to 120° C. and 10^{-1} mm. Hg. corresponding to a yield over 59% of the theoretical.

Elemental analysis

Calculated for $C_{16}H_{29}N_3$ (263):	Found
C: 72.9%	C: 72.5%
H: 11.1%	H: 11.0%
N: 16.0%	N: 15.7%

Manufacture of a composition containing

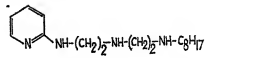


10 parts by weight of the above compound, 10 parts by weight of the addition product of 10 mols of ethylene oxide with 1 mol of nonyl phenol, 8 parts by weight of tartaric

acid, 50 parts by weight of ethyl glycol, 3 parts by weight of hydroxyethyl cellulose and 119 parts by weight of water give on heating to approximately 50° C. with stirring, a viscous, homogeneous preparation with 5% active substance which can be mixed with water in any proportion.

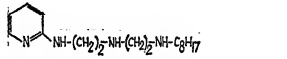
Example 3

Preparation of



1 mol of 2-bromopyridine, 2 mols of n-octyldiethylene triamine, 0.3 mol of water and 1.5 mols of potassium hydroxide are heated for 16 hours to a maximum temperature of 180° C. with slow distillation of water. After analogous treatment as in Example 2, the above compound is obtained in a yield of 63% of the theoretical as a light-yellow oil distilling at 170 to 180° C. and 10^{-3} to 10^{-4} mm.Hg. The elemental analysis confirms the above structure.

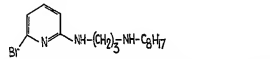
Manufacture of a composition containing



10 parts by weight of the above compound, 10 parts by weight of the addition product of 12 mols of ethylene oxide with 1 mol of isotridecyl alcohol, 10 parts by weight of acetic acid, 20 parts by weight of ethanol and 50 parts by weight of water are homogenized with stirring and heating to approximately 40° C., when a clear solution with 10% active substance is obtained.

Example 4

Preparation of



1 mol of 2,6-dibromopyridine, 1.5 mols of N-n-octylpropylene diamine, 1.6 mols of sodium hydroxide and 0.2 mol of water are heated for 2 hours to 130° C.. The mixture is then decanted off the inorganic residue while still hot and non-reacted N-octyl-propylene diamine is separated by fractional distillation. The residue is purified by means of a molecular distillation apparatus. At a heating bath temperature of 120 to 160° C. and a pressure of 10^{-2} to 5.10^{-3} mm.Hg. altogether 295 g. of the pure product of the above formula distil over to give a yield of 85% of the theoretical.

Elemental analysis

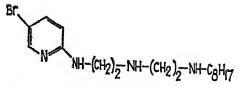
Calculated for $C_{16}H_{28}N_2Br$ (342):	Found:
C: 56.1%	C: 56.4%
H: 8.2%	H: 8.5%
N: 12.3%	N: 12.5%
Br: 23.4%	Br: 23.0%

Manufacture of a composition containing

20 parts by weight of the above compound, 15 parts by weight of acetic acid, 20 parts by weight of the addition product of 12 mols of ethylene oxide with 1 mol of isotridecyl alcohol, 100 parts by weight of ethyl glycol and 145 parts by weight of water are homogenized with slight heating and stirring. A clear solution that is miscible with water is obtained.

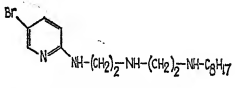
Example 5

Preparation of



0.5 mol of 2,5-dibromopyridine, 1.5 mols of N-n-octyldiethylene triamine, 0.7 mol of sodium hydroxide and 0.1 mol of water are heated for 12 hours to 170° C. with slow distillation of water. After analogous treatment to that described in Example 4, a yield of 73% of the theoretical of pure product of the above formula is obtained.

Manufacture of a composition containing

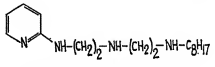


5 parts by weight of the above compound, 5 parts by weight of the addition product of 12 mols of ethylene oxide with 1 mol of isotridecyl alcohol, 4 parts by weight of acetic acid, 30 parts by weight of propylene glycol and 156 parts by weight of water are homogenized with stirring and heating to 50° C. A composition is obtained which is miscible in any proportions with water and which has an active substance content of 2.5%.

I. Bacteriological tests

The execution of the tests took place in accordance with the directives of the Deutsche Gesellschaft für Hygiene und Mikrobiologie.

1) Test substance in accordance with the invention (according to Example 3)

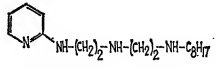


a) Suspension test
pH: 7 (Dilution stage containing 0.1% active substance)

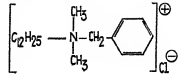
Test strain	Concentration in %	Duration of action in minutes 1	2	5	10	20	30
Staphylococcus aureus	0.1	–	–	–	–	–	–
	0.05	–	–	–	–	–	–
	0.01	+	–	–	–	–	–
Pseudomonas aeruginosa	0.1	–	–	–	–	–	–
	0.05	–	–	–	–	–	–
	0.01	+	+	–	–	–	–
Proteus vulgaris	0.1	–	–	–	–	–	–
	0.05	–	–	–	–	–	–
	0.01	+	+	–	–	–	–
Escherichia coli	0.1	–	–	–	–	–	–
	0.05	–	–	–	–	–	–
	0.01	+	–	–	–	–	–

b) Determination of the bacteriological activity in the presence of albumin (20% cattle serum)

A) Test substance in accordance with the invention (according to Example 3)



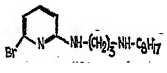
10 B) *Comparison substance* quaternary ammonium compound of formula 10



Test strain	Concentration in %	Duration of action in minutes 1	2	5	10	20	30	Duration of action in minutes 1	2	5	10	20	30
Staphylococcus aureus	0.1	–	–	–	–	–	–	+	–	–	–	–	–
	0.05	+	+	–	–	–	–	+	+	+	–	–	–
	0.01	+	+	+	+	+	+	+	+	+	+	+	+
Pseudomonas aeruginosa	0.1	–	–	–	–	–	–	+	+	+	+	+	+
	0.05	–	–	–	–	–	–	+	+	+	+	+	+
	0.01	+	+	+	+	+	+	+	+	+	+	+	+
Proteus vulgaris	0.1	–	–	–	–	–	–	+	+	+	–	–	–
	0.05	–	–	–	–	–	–	+	+	+	+	+	–
	0.01	+	+	+	+	+	+	+	+	+	+	+	+
Escherichia coli	0.1	–	–	–	–	–	–	+	–	–	–	–	–
	0.05	–	–	–	–	–	–	+	+	+	+	+	–
	0.01	+	+	+	+	+	+	+	+	+	+	+	+

A comparison of the bacteriological effectiveness shows immediately the superiority of the test substance in accordance with the invention over the quaternary ammonium compound serving as comparison substance and representing the prior art.

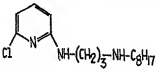
2) a) Test substance in accordance with the invention (according to Example 4)



Suspension test

pH: 5 (0.1% active substance contained in dilute material)

b) *Comparison substance* (according to Patent Specification No. 1,298,054)

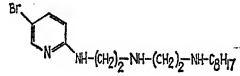


pH: 5 (0.1% active substance in dilute material)

Test stain	Concentration in %	Duration of action in minutes 1	2	5	10	20	30	Duration of action in minutes 1	2	5	10	20	30
Staphylococcus aureus	0.1	–	–	–	–	–	–	–	–	–	–	–	–
	0.05	–	–	–	–	–	–	–	–	–	–	–	–
	0.01	+	+	–	–	–	–	+	+	+	–	–	–
Pseudomonas aeruginosa	0.1	–	–	–	–	–	–	–	–	–	–	–	–
	0.05	–	–	–	–	–	–	–	–	–	–	–	–
	0.01	–	–	–	–	–	–	+	+	+	+	+	+
Proteus vulgaris	0.1	–	–	–	–	–	–	–	–	–	–	–	–
	0.05	–	–	–	–	–	–	+	–	–	–	–	–
	0.01	+	+	–	–	–	–	+	+	+	+	+	–
Escherichia coli	0.1	–	–	–	–	–	–	–	–	–	–	–	–
	0.05	–	–	–	–	–	–	–	–	–	–	–	–
	0.01	–	–	–	–	–	–	+	+	+	+	–	–

A comparison of the bacteriological effectiveness of the above compounds clearly indicates the superiority of the compound in accordance with the invention.

3) Test substance in accordance with the invention (according to Example 5)



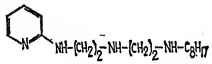
Suspension Test

pH: 5.5 (0.1% active substance in dilute material)

Test strain	Concentration in %	Duration of action in minutes 1	2	5	10	20	30
Staphylococcus aureus	0.1	—	—	—	—	—	—
	0.05	–	–	–	–	–	–
	0.01	–	–	–	–	–	–
	0.005	+	+	–	–	–	–
Pseudomonas aeruginosa	0.1	–	–	–	–	–	–
	0.05	–	–	–	–	–	–
	0.01	–	–	–	–	–	–
	0.05	+	+	+	–		–
Proteus vulgaris	0.1	–	–	–	–	–	–
	0.05	–	–	–	–	–	–
	0.01	–	–	–	–	–	–
	0.005	+	+	–	–	–	–
Escherichia coli	0.1	–	–	–	–	–	–
	0.05	–	–	–	–	–	–
	0.01	+	+	+	–	–	–

II. Eye irritation tests of rabbits according to Draize
(J. H. Draize and E. A. Kelley; Drug and Cosmetic Ind., *71* 1952, 36—37 and 118—120

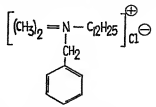
1) *Test substance in accordance with the invention*



pH: 6 (Solution containing 0.5% active substance)

Rabbit No.		1	2	3	4	5	6	Mean value
1st day	A	1	1	2	1	2	1	
	B	1	2	1	1	1	1	
	C	1	1	1	1	1	1	
		3×3=6	4×2=8	4×2=8	3×2=6	4×2=8	3×2=6	7
2nd day	A	1	0	1	1	1	1	
	B	0	1	1	0	1	0	
	C	0	0	0	0	0	0	2.7
		1×2=2	1×2=2	2×2=4	1×2=2	2×2=4	1×2=2	
3rd day	A	0	0	1	0	1	0	
	B	0	0	0	0	0	0	
	C	0	0	0	0	0	0	
		0	0	1×2=2	0	1×2=2	0	0.7
4th day	A	0	0	0	0	0	0	
	B	0	0	0	0	0	0	
	C	0	0	0	0	0	0	0

2) *Comparison substance* quaternary ammonium compound of formula:



in aqueous solution containing 0.5% active substance

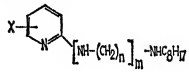
Rabbit No.		1	2	3	4	5	6	Mean value
1st day	A	3	3	3	3	3	3	
	B	2	3	2	3	3	2	
	C	2	3	2	3	3	2	
		7×2=14	9×2=18	7×2=14	9×2=18	9×2=18	7×2=14	16
2nd day	A	2	3	2	3	2	2	
	B	2	2	2	2	2	2	
	C	2	2	2	2	2	1	
		6×2=12	7×2=14	6×2=12	7×2=14	6×2=12	5×2=10	12.3
3rd day	A	2	2	1	2	2	1	
	B	1	2	1	2	1	1	
	C	1	1	1	1	1	1	
		4×2=8	5×2=10	3×2=6	5×2=10	4×2=8	3×2=6	8

Rabbit No.	1	2	3	4	5	6	Mean value
4th day A	1	1	1	2	1	1	
B	1	1	1	1	0	0	
C	0	1	0	1	1	0	
	2×2=4	3×2=6	2×2=4	4×2=8	2×2=4	1×2=2	4.7
5th day A	1	1	1	1	1	0	
B	0	1	0	1	0	0	
C	0	0	0	0	0	0	
	1×2=2	2×2=4	1×2=2	2×2=4	1×2=2	0	2.3
6th day A	0	1	0	7	0	0	
B	0	0	0	0	0	0	
C	0	0	0	0	0	0	
	0	1×2=2	0	1×2=2	0	0	0.7
7th day A	0	0	0	0	0	0	
B	0	0	0	0	0	0	
C	0	0	0	0	0	0	0

A comparison of the eye irritation effect of the compound in accordance with the invention with the quaternary ammonium compound representing the prior art shows the highly significant smaller irritation effect of the compound in accordance with the invention (smaller numerical value of the mean).

WHAT WE CLAIM IS:—

1. A compound of the general formula



wherein X is a hydrogen atom or a bromine atom which may be in the 5 or 6 position of the pyridine ring, n is 2 or 3 and m is 0, 1 or 2.

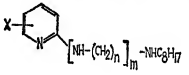
2. A compound of the general formula defined in Claim 1 substantially as hereinbefore described in any one of the foregoing Examples.

3. A biocidal composition comprising a compound as claimed in Claim 1 or 2 and a solid or liquid diluent or carrier therefor.

4. A composition as claimed in Claim 3, wherein the preparation additionally comprises one or more of a solvent, a surfactant, a thickener, a filler, urea, cane sugar, cellulose, an odorant and colorant.

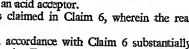
5. A biocidal composition in accordance with Claim 3 substantially as hereinbefore described in any one of the foregoing Examples.

6. A process for the preparation of a compound of the general formula



where X is a hydrogen atom or a bromine atom which may be in the 5 or 6 position of the pyridine ring, n is 2 or 3 and m is 0, 1 or 2, wherein 1 mol of a compound of the general formula

where Y is a chlorine or bromine atom is reacted with 1 to 4 mols of an amine of the general formula



where X, n and m have the meanings defined above, at a temperature of 100 to 180° C. in the presence of an acid acceptor.

7. A process as claimed in Claim 6, wherein the reaction is carried out in the presence of a solvent.

8. A process in accordance with Claim 6 substantially as hereinbefore described in any one of the foregoing Examples.

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